(b)4 - Confidential Business

3. Pharmacokinetics/Statistics:

The concentration of acyclovir measured at each time point after each product is summarized in Table 1. The time courses of acyclovir concentration after the three treatments are plotted in Figures 1 and 2. These data indicate that with the exception of 0.33 and 0.67 hour samples, acyclovir plasma concentrations following administration of the test product (fed) were within 20% of that of the reference product (fed). When the test and reference formulations were administered after a meal, the least squares means for AUC_{0-t}, and AUC_{0-inf} for test formulation were 3% and 4% lower than the respective means for reference formulation. The mean C_{max} for test product was 6% lower than that of the reference product and occurred 5% (7 minutes) later (Table 2).

Based on least squares means, following are the ratios of the means of the pharmacokinetic parameters:

	Ratio of means (test/reference)
Test (Fed) vs. Reference (Fed)	
AUC_{0-t}	0.96
AUC_{0-inf}	0.96
C_{max}	0.94
Test (Fed) vs. Test (Fasted)	
AUC_{0-t}	1.16
AUC_{0-inf}	1.13
C_{max}	1.06

The least squares means for AUC_{0-t} and AUC_{0-inf} after the meal were 14% higher compared to fasting. The mean C_{max} was 5% higher and 24% (33 minutes) later in test fed compared to test fasting conditions (Table 2).

The firm has provided 90% confidence interval values:

AUC_{0-t}	82.4%-109%
AUC_{0-inf}	83.2%-107%
C_{max}	79.4%-106%

The 90% confidence interval values for C_{max} are outside the 80%-125% limits. However, this is not a requirement for a limited

food study. Ratios of means between test and reference fed are within the acceptable limits of 0.80-1.20.

Comments:

1. Eighteen subjects entered the study. Subject #18 failed to return after completing period I, subject #5 and 9 did not return for period III. Subject #8 was withdrawn from the study by the physician because at the entry of phase III (0 hour) his blood pressure measurements were 160/102. At the end of phase II (48 hour), his blood pressure readings were 114/77. Six subjects reported a total of 10 adverse events. All of the events were mild in nature. Two subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation.

2. The clinical and analytical site for fasting study was (b)4 - Confidential Clinical study dates were: phase I September 24-26, 1994 and phase II October 1-3, 1994. The sample analysis dates were October 8-29, 1994. The clinical site for the fed study was (b)4 - Confidential and it was conducted from January 31 to February 16, 1995. However, the sample analysis did not begin until November 14, 1995 and the analyses were done at (b)4 - Confidential

3. The predose sample (0 hr) of subject #14 had acyclovir concentration of 79.7 ng/mL for dosing period II (Test-Fed).[The 24 hr sample (last) in period I of this subject had 0 ng/mL acyclovir plasma concentration]. The analysis could not be repeated because of insufficient sample. The 0.33 hr sample had no quantifiable plasma acyclovir concentration. The firm used reported value (79.7 ng/mL) in the calculations and statistical analysis.

4. When the test and reference formulations were administered after a meal, the least squares means for AUC_{0-t}, and AUC_{0-inf} for test formulation were 3% and 4% lower than the respective means for reference formulation. The mean C_{max} for test product was 6% lower than that of the reference product and occurred 5% (7 minutes) later. The test/reference ratios for mean AUC_{0-t}, AUC_{0-inf}, and C_{max} are all within the 0.8-1.2 limit.

5. The least squares means for AUC_{0-t} and AUC_{0-inf} after the meal were 14% higher compared to fasting. The mean C_{max} was 5% higher and 24% (33 minutes) later in test fed compared to test fasting conditions.

6. The fasting study and dissolution data submitted earlier by the firm are acceptable.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fed conditions by Zenith Laboratories, Inc. on its 200 mg acyclovir capsules, lot #ND-244, comparing it to the reference listed drug, Zovirax® capsules 200 mg, lot #4N2584 manufactured by Burroughs Wellcome has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Zenith's acyclovir 200 mg capsule is similar to that of the reference product Zovirax® 200 mg capsule manufactured by Burroughs Wellcome.

2. The *in vivo* bioequivalence study previously conducted under fasting conditions by Zenith Laboratories on its 200 mg acyclovir capsules, lot #ND-244, comparing it to the reference listed drug, Zovirax® capsules 200 mg, lot #4N2584 manufactured by Burroughs Wellcome had been found acceptable to the Division of Bioequivalence. The study demonstrated that under fasting conditions, Zenith's acyclovir 200 mg capsule is bioequivalent to the reference product Zovirax® 200 mg capsule manufactured by Burroughs Wellcome.

3. The dissolution testing previously conducted on acyclovir 200 mg capsule was acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be done in 900 mL of water at 37°C using apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

> Not less than (b)4 of the labeled amount of acyclovir in the dosage form is dissolved in **30** minutes.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

/S/ 1/26/96
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

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FT INITIALED S.NERURKAR

/S/ Date 5/3/96

Table 1

Acyclovir Plasma Concentrations (ng/mL) (n=14) in the Food Study: Arithmetic Means ± Standard Deviation

Time	Test-Fed	Ref-Fed	Test-fasted			
h	A	B	C	A/B	A/C	B/C
0	5.69±21.3	0	0			
0.33	12.12±37.4	2.40±8.9	45.66±64.26	5.05	0.26	0.05
0.67	91.20±128.6	69.76±110.3	302.3±199.0	1.31	0.30	0.23
1	234.7±155.4	254.1±171.9	497.1±183.4	0.92	0.47	0.51
1.33	392.2±169.2	441.9±158.4	553.6±163.9	0.89	0.71	0.80
1.67	537.7±209.7	566.0±135.5	552.8±171.3	0.95	0.97	1.02
2	595.1±217.2	622.7±132.8	563.6±218.9	0.96	1.06	1.10
2.5	578.0±205.6	629.8±135.6	517.7±227.0	0.92	1.12	1.22
3	557.7±202.9	614.8±146.1	466.9±212.8	0.91	1.19	1.32
3.5	547.3±224.8	558.3±249.4	402.4±215.9	0.98	1.36	1.39
4	510.6±271.2	519.7±256.6	364.2±181.9	0.98	1.40	1.43
5	405.2±221.7	408.3±206.7	285.6±156.9	0.99	1.42	1.43
6	297.3±164.0	310.7±180.2	219.4±142.4	0.96	1.35	1.42
8	185.7±98.9	183.9±92.9	133.3±73.6	1.01	1.39	1.38
10	119.6±58.9	122.9±67.7	92.9±48.4	0.97	1.29	1.32
12	77.6±41.2	81.9±46.9	64.6±28.9	0.95	1.20	1.27
14	55.1±35.7	54.2±38.7	44.1±22.2	1.02	1.25	1.23
16	36.2±25.7	36.9±27.9	32.0±18.6	0.98	1.13	1.15
24	12.5±16.3	13.4±18.5	11.9±15.1	0.93	1.05	1.13
Parameters						
AUC_{0-t} (ng/mLxh)	3797±1607	3919±1491	3284±1376	0.97	1.16	1.19
AUC_{0-inf} (ng/mLxh)	3983±1667	4134±1556	3531±1381	0.96	1.12	1.17
C_{max} (ng/mL)	685±243	729±193	649±234	0.94	1.05	1.12
T_{max} (h)	2.274±0.88	2.143±0.80	1.726±0.55	1.06	1.32	1.24
½ life (h)	4.194±1.5	4.164±1.69	5.858±3.9	1.01	0.71	0.71
KELM (h^{-1})	0.184±0.06	0.189±0.06	0.154±0.06	0.97	1.19	1.23

Table 2

Acyclovir Plasma Concentrations in the Food Study (n=14)
Pharmacokinetic Parameters: Least Square Means ± Standard Error

Parameter	Test-Fed A	Ref-Fed B	Test-Fasted C	A/B	A/C	B/C
AUC_{0-t} (ng/mLxh)	3794±199	3929±199	3276±199	0.96	1.16	1.20
AUC_{0-inf} (ng/mLxh)	3981±192	4144±192	3526±192	0.96	1.13	1.17
C_{max} (ng/mL)	680±36	725±36	643±36	0.94	1.06	1.13
T_{max} (h)	2.294±0.18	2.169±0.178	1.737±0.178	1.06	1.32	1.25
$LNAUC_{0-t}$	8.163±0.057	8.218±0.057	8.022±0.057	0.99	1.02	1.02
$LNAUC_{0-inf}$	8.213±0.052	8.272±0.052	8.104±0.052	0.99	1.01	1.02
LNC_{max}	6.476±0.060	6.561±0.060	6.408±0.060	0.99	1.01	1.02

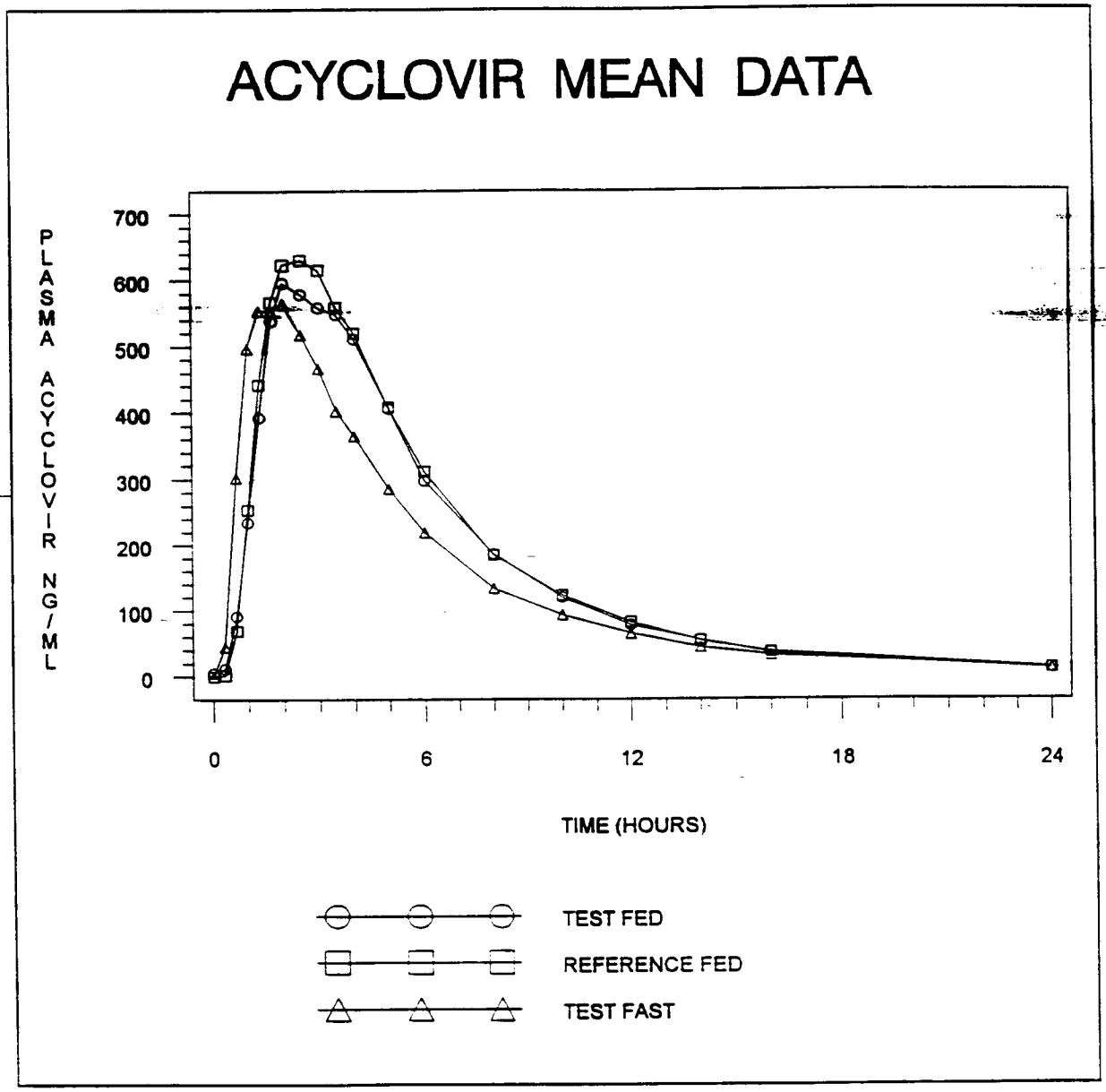

ACYCLOVIR MEAN DATA
PLASMA ACYCLOVIR NG/ML
700
600
500
400
300
200
100
0
0
6
12
18
24
TIME (HOURS)
TEST FED
REFERENCE FED
TEST FAST

figure 1

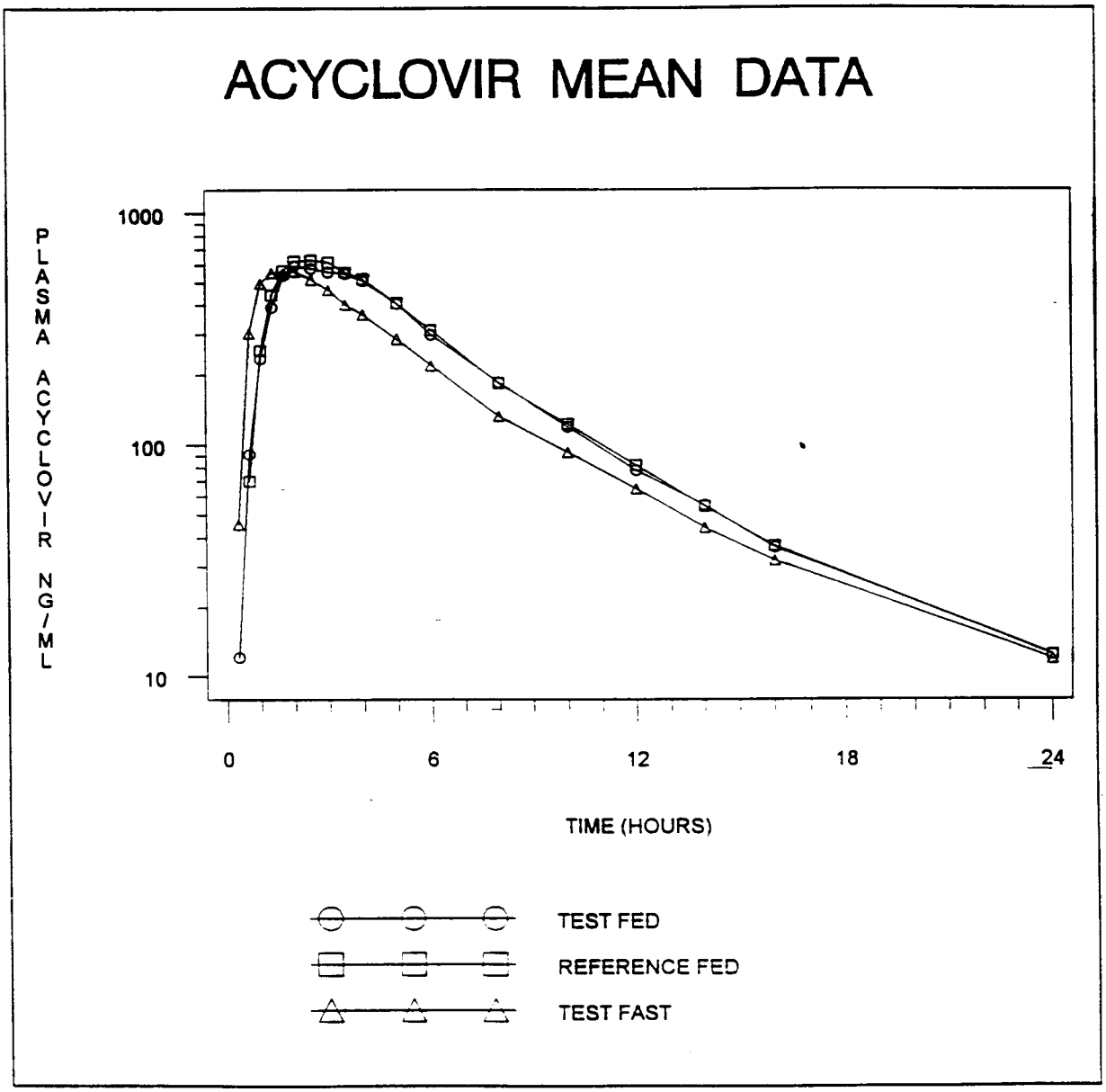

ACYCLOVIR MEAN DATA
PLASMA ACYCLOVIR NG/ML
1000
100
10
0
6
12
18
24
TIME (HOURS)
TEST FED
REFERENCE FED
TEST FAST

Figure 2

Acyclovir Capsules, 200 mg
ANDA 74-674

NOV 13 1995

Zenith Laboratories, Inc.
Attention: Robert J. Monaghan
140 Legrand Avenue
Northvale, NJ 07647

Dear Mr. Monaghan:

Reference is made to the *in vivo* bioequivalence study submitted on May 22, 1995 for Acyclovir Capsules, 200 mg.

The Office of Generic Drugs (OGD) has reviewed the submitted bioequivalence data and the following comments are provided for your consideration:

Since the Agency has data which demonstrates food may affect bioavailability, as a condition of approval both fasting and non-fasting studies are required. Until the non-fasting study is submitted the bioequivalence data will be considered incomplete.

As described under 21 CFR 314.96 an action which will amend this application is required. Your response to this correspondence will be considered a major amendment. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In any future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 4 1995

Acyclovir
200 mg Capsule
ANDA #74-674
Reviewer: Kuldeep R. Dhariwal
File Name: 74674SD.595

Zenith Laboratories, Inc.
140 Legrand Avenue
Northvale, NJ 07647
Submission Date:
May 22, 1995

Review of Bioequivalence Study and Dissolution Data

The firm has submitted a single-dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its acyclovir capsules, 200 mg with Burroughs Wellcome's Zovirax® capsules, 200 mg. Each dose consisted of 400 mg (2 capsules) of either the test or reference product.

Introduction:

Acyclovir, 9-[(2-hydroxyethoxy)methyl]guanine is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 and 2, varicella-zoster virus, Epstein-Barr virus and cytomegalovirus. The inhibitory activity of acyclovir for these viruses is highly selective, involving preferential uptake into virus-infected cells and requiring a virus-specific thymidine kinase for conversion to the monophosphate. Subsequent conversion to the triphosphate results in irreversible binding to DNA polymerase and termination of DNA replication.

The absorption of acyclovir in humans after its oral administration is slow, variable, and incomplete. The absolute bioavailability from different studies involving both normals and patients is reported to be 15-30%. In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities were 20%, 15%, and 10% respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In another study, the influence of food on the absorption of acyclovir was not apparent.

The reference product is Zovirax® available as 200 mg capsule, 400 mg and 800 mg tablets, and as 200 mg per 5 mL suspension. It is marketed by Burroughs Wellcome.

Bioavailability of Acyclovir Capsules, 200 mg under Fasting Conditions:

A. Objective:

The objective of this study is to compare the acyclovir plasma levels produced after administration of test formulation with those produced after administration of a marketed reference product, under fasting conditions.

B. Study Sites and Investigators:

Clinical and Analytical Site: (b)4 - Confidential Business,
Principal Investig (b)4 - Confidential
Project Director: Business
Protocol #10683 "Bioavailability of Acyclovir Capsules, 200 mg" was approved by National Institutional Review Board for (b)4 - Confidential Business
Consent Form: A copy of volunteer informed consent form used in the study is given on page 75, vol. 1.1.
Study #037-65-10683
Study Dates: Phase I September 24-26, 1994
Phase II October 1-3, 1994
Analysis Dates: October 8-29, 1994

C. Study Design:

The protocol was designed as a single-dose, randomized, two-way crossover bioavailability study. The study was executed in two phases with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours postdose each phase. The subjects were assigned to two groups at random as follows:

Group	Subject number	Phase I	Phase II
1	1,4,5,8,10,12,13,15,18,20, 22,24,25,28,30,31	A	B
2	2,3,6,7,9,11,14,16,17,19, 21,23,26,27,29,32	B	A

Subject # 9,14,15,31, and 32 did not complete the study.

A: Acyclovir Capsules, 2 X 200 mg, Zenith Laboratories, Inc.; Lot # ND-244; Lot size: Theoretical Yield (b)4 - Confidential (b)4 - Expiration Date: 9/96 (proposed); Manufacture Date:8/94; Assay: 99.3%; Uniformity of dosage units: 97.6%.

B: Zovirax® Capsules, 2 X 200 mg, Burroughs Wellcome Co.; Lot # 4N2584; Expiration Date: 3/97; Assay: 99.9%; Uniformity of dosage units: 98.4%.

The subjects fasted for no less than 10 hours prior to drug administration and until 5 hours postdose. Fluids were restricted within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to lie down for 4 hours postdose. Identical meals were served during both housing periods. Blood pressure and pulse measurements were obtained predose, and at 4 and 24 hours postdose. Diagnostic blood and urine specimens were obtained at 16 hours postdose phase II (at the end of the study).

D. Subject Selection:

Thirty-two healthy male subjects were enrolled in the study. Blood samples from all subjects who completed the study were to be analyzed. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ± 15% from ideal weight for his height as defined by Metropolitan Life Insurance Company Statistical Bulletin, 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study.

Subjects were excluded from this study based on the following criteria:

- history of asthma, chronic bronchitis, hypertension, cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV 1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to acyclovir or to related drugs

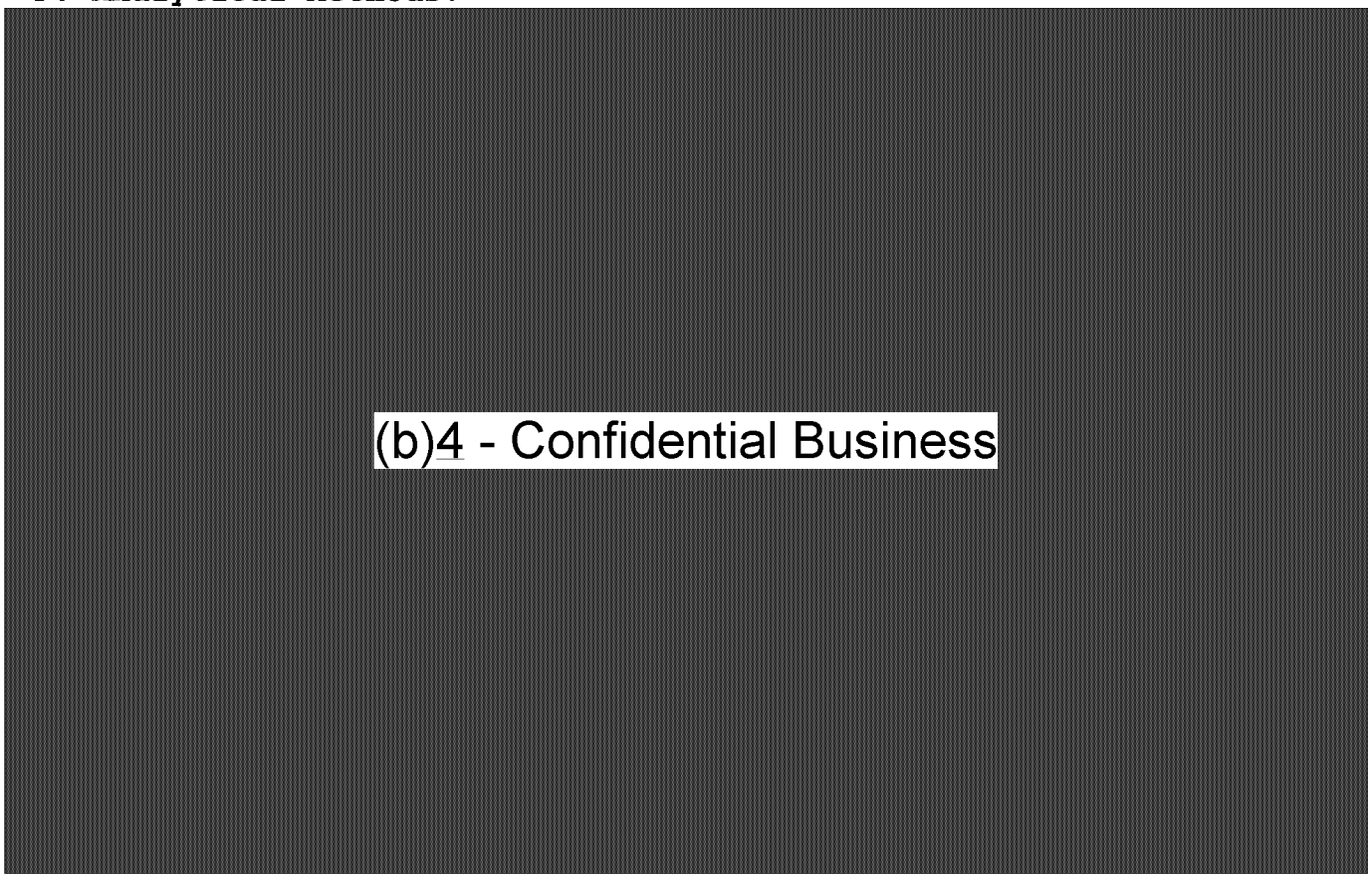
Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding OTC analgesics, vitamins, medicated lozenges, dietary supplements) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration, each phase
- no caffeine for at least 12 hours prior to dosing
- a curfew of 11 p.m. was observed for the nights prior to dosing, and a curfew of 1 a.m. was observed for all other nights
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- no strenuous physical activity will be permitted during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers at 0 (predose), 0.33,0.67,1,1.33,1.67,2,2.5,3,3.5, 4,5,6,7,8,10,12,14, and 16 hours postdose. Samples were centrifuged within 15 minutes of venipuncture at 10°C for 15 minutes at 2500 rpm. After centrifugation, the plasma was transferred into prelabeled polypropylene tubes and stored at -20°C until they were transferred to the analytical laboratory on October 6, 1994.

F. Analytical Methods:



G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last five concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means

were calculated using the least squares means and the standard error of the estimate of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Thirty-two subjects entered the study. Five subjects failed to return to the facility to complete phase II. Samples from twenty-seven subjects who completed the study were analyzed. Clinical vital signs were measured before dosing and at 4 and 24 hours after dosing. The firm has provided the measurements in a tabular form. The reviewer plotted mean systolic and diastolic blood pressure. There was no significant difference in these parameters between the test and reference formulations.

Adverse events:

Following five subjects experienced adverse events during the study for which no medication was required:

Subject #	Phase	Product	Sign/Symptom
1	I	Test	Headache
5	I	Test	Lightheaded
22	II	Reference	Generalized headache
23	II	Test	Sore throat, congestion
28	*	Test	Headache

* headache on 9/28/94 from 9.00 a.m. to 3.00 p.m., resolved within 6 hours without any medication (subject reported this event at entry of phase II on 10/1/94.

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation. The firm states that attempts are continuing to contact these subjects for follow-up.

Subject #	Test result
2	Low hemoglobin and hematocrit
10	High triglycerides
16	High white blood cell count and triglycerides abnormal urinalysis
19	Abnormal urinalysis
21	High blood glucose
30	Blood in urine

Deviations in the study:

No deviations from the scheduled phlebotomy time or in sample processing were reported.

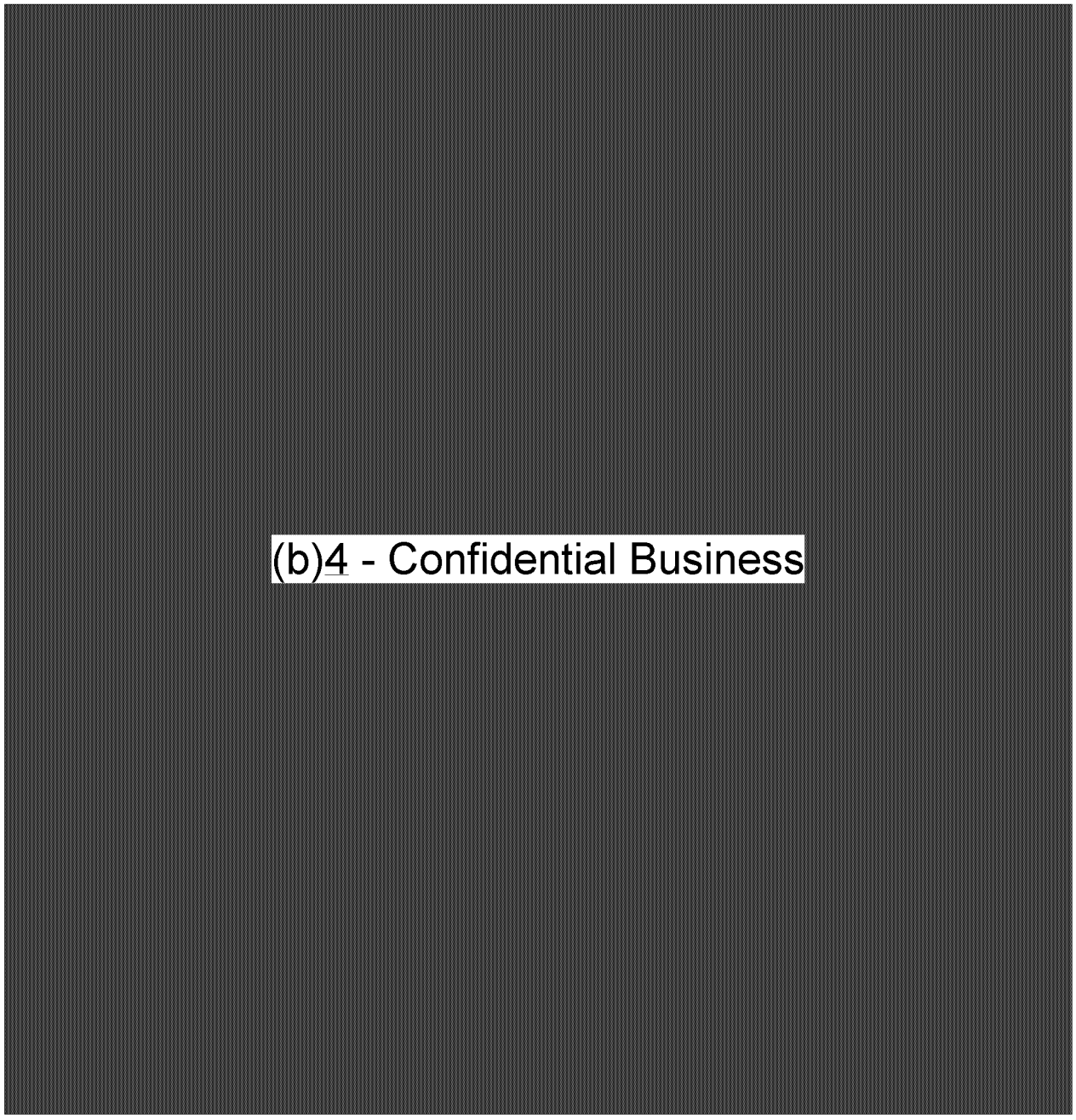
Reassays: Of the 1026 samples assayed for this study, 38 samples (3.7%) were reassayed. Following samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
20	[redacted]/(b)4 -[redacted]anomaly i.e., a concentration value which differs markedly from the routine pharmacokinetic profile
13	Chromatographic interference
3	Suspected processing error
2	To confirm the presence of peak at the retention time of the drug

2. Analytical:

[redacted]

(b)4 - Confidential Business



3. Pharmacokinetics/Statistics:

The mean plasma concentrations of acyclovir at each time point after test and reference products are shown in Table 1. There is no significant (α =0.05) difference in mean concentrations between the formulations at any time after dosing. The time courses of acyclovir concentration after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Table 2. There is no statistically significant difference between the two formulations for any parameter. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and AUC_{0-inf} for the test product are 5% and

4% lower than the respective estimates for the reference product. The C_{max} for the test product was 3% lower than that for the reference product and occurred 12 minutes later.

The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Acyclovir (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
7	1646.8	2004.8	1647	2005
12	1947.2	2225.5	1947	2225
27	3410.9	4181.6	3411	4181

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual mean ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 3. The test/reference ratio for AUC_{0-t} ranged from 0.475 to 1.829 (mean 1.012), AUC_{0-inf} ranged from 0.600 to 1.604 (mean 1.005) and for C_{max} ranged from 0.545 to 1.821 with a mean of 1.029.

Table 4 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from 0.55 to 0.94 (24 out of 26 values between 0.80 and 0.94) for test and 0.66 to 0.94 (24 out of 27 values between 0.80 and 0.94) for reference product.

The following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	85.0-107.0	84.68-106.55
$LNAUC_{0-inf}$	87.0-106.0	86.81-105.84
LNC_{max}	86.0-109.0	85.86-108.86

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125. Statistical analysis of the data did not show any significant treatment or period effect for AUC_{0-t}, AUC_{0-inf}, and C_{max}. However, there was statistically significant ($p < 0.10$) sequence effect for C_{max} ($p=0.0730$).

Plasma acyclovir concentration for subject #6 after the test product did not decline smoothly over time. Therefore,

elimination rate constant, half-life and AUC_{0-inf} for test product were calculated using data from remaining subjects (26). The same parameters for reference product were calculated using data from all subjects (27).

In Vitro Dissolution Testing:

The firm has submitted comparative dissolution data for test and reference products using FDA dissolution method. No USP dissolution method is available at this time. The dissolution testing was done in 900 mL water using apparatus 1 (basket) at 100 rpm. The capsules used in the dissolution tests were from the same lot used in the *in vivo* bioequivalence study. The firm has set its specifications as NLT (b)4 - Q) in 60 minutes. The agency's specifications are NLT (b)4 - Q) in 30 minutes. The results of dissolution tests show that at 30 minutes, 10 test capsules dissolved more than (b)4 and 2 capsules dissolved less than (b)4 The dissolution results of firm's individual capsules at 30 minutes are (%): 94.0, 90.6, 99.4, 92.0, 83.6, 93.3, 100.3, 95.9, 92.7, 96.5, 93.9, and 81.3. However, these results pass the acceptance criteria: average of 12 units (92.8%) is equal to or greater than Q (b)4 - and no unit is less than Q-15%.

Comments:

1. Thirty-two subjects entered the study. Five subjects failed to return to the facility to complete phase II. Samples from twenty-seven subjects who completed the study were analyzed. Five subjects experienced adverse events like headache during the study for which no medication was required. Six subjects showed post-study laboratory results outside of the reference range. The firm states that attempts are continuing to contact these subjects for follow-up.

2. Based on the least squares means of the logarithmically transformed parameters, the AUC_{0-t} and AUC_{0-inf} for the test product were 5% and 4% lower than the respective estimates for the reference product. The C_{max} for the test product was 3% lower than that for the reference product and occurred 12 minutes later. The 90% confidence intervals for log transformed data for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125.

4. There were no statistically significant treatment or period effects for AUC_{0-t}, AUC_{0-inf}, and C_{max}. However, there was statistically significant ($p < 0.10$) sequence effect for C_{max} ($p=0.0730$). The study is acceptable as it meets the requirements given in division's guidance: statistical procedures for bioequivalence studies using a standard two-treatment crossover design, for studies showing a statistically significant sequence effect.

5. The dissolution testing was done using FDA method. The results of dissolution tests show that at 30 minutes, 10 test capsules dissolved more than (b)4 - and 2 capsules dissolved less than (b)4 - . However, these results pass the acceptance criteria: average of 12 units (92.8%) is equal to or greater than Q (b)4 - and no unit is less than Q-15%. The results of dissolution tests are acceptable.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Zenith Laboratories Inc. on its 200 mg Acyclovir capsules, lot #ND-244, comparing it to the reference listed drug, Zovirax® capsules 200 mg, lot #4N2584 manufactured by Burroughs Wellcome has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Zenith's Acyclovir 200 mg capsule is bioequivalent to the reference product Zovirax® 200 mg capsule manufactured by Burroughs Wellcome.

2. The dissolution testing conducted on Acyclovir 200 mg capsule is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be done in 900 mL of water at 37°C using apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

> Not less than (b)4 - of the labeled amount of Acyclovir in the dosage form is dissolved in 30 minutes.

3. The firm has not submitted limited food study data using three-way crossover study design. A limited food study is required for product approval. Therefore, from bioequivalence standpoint the firm has not met the *in vivo* bioavailability requirements and the application is not approvable. The firm should be requested to submit a fed study on this drug product.

4. The firm may be informed to submit both fasted and fed studies together if it is required for a drug product.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

Table 1

Mean Acyclovir Plasma Concentrations (ng/mL) (N=27)
Arithmetic Means and Standard Deviation (SD)

Time (h)	Test		Reference		Test/Ref	Significance at p=0.05
	Mean	SD	Mean	SD		
0	0.0		0.0			
0.33	52.34	73.46	28.52	56.19	1.84	N.S.
0.67	305.3	188.5	293.7	140.1	1.04	N.S.
1	446.9	206.9	449.0	155.7	1.00	N.S.
1.33	488.2	184.9	552.1	168.4	0.88	N.S.
1.67	515.7	179.1	576.4	168.2	0.89	N.S.
2	527.3	195.1	578.6	177.9	0.91	N.S.
2.5	469.0	159.1	513.6	150.4	0.91	N.S.
3	406.1	135.2	463.2	160.4	0.88	N.S.
3.5	370.9	120.1	401.1	135.5	0.92	N.S.
4	330.8	112.9	342.9	111.3	0.96	N.S.
5	272.4	120.9	269.6	89.22	1.01	N.S.
6	201.9	80.21	198.9	60.13	1.02	N.S.
7	159.3	58.25	162.6	55.61	0.98	N.S.
8	125.4	43.00	128.0	39.78	0.98	N.S.
10	81.84	39.56	84.69	40.27	0.97	N.S.
12	45.58	43.64	44.36	37.99	1.03	N.S.
14	20.87	35.37	19.60	31.55	1.06	N.S.
16	10.00	25.06	6.507	18.84	1.54	N.S.

Table 2

Acyclovir Plasma Concentrations: Pharmacokinetic Parameters
Least Square Means ± Standard Error

Parameter	Test	Reference	Test/Ref	Confidence Interval
AUC_{0-t} (ng/mLxh)	2757±124.1	2884±124.1	0.96	0.85-1.06
AUC_{0-inf} (ng/mLxh)	3152±131.7	3266±126.4	0.95	0.85-1.07
C_{max} (ng/mL)	620±29.41	641±29.4	0.97	0.86-1.08
Half-life (h)	4.096±0.29	3.984±0.27	1.03	0.86-1.20
T_{max} (h)	1.913±0.15	1.717±0.15	1.11	
Rate Constant (h^{-1})	0.199±0.008	0.199±0.008	1.00	
$LNAUC_{0-t}$	7.876±0.048	7.927±0.047	0.95	0.85-1.07
$LNAUC_{0-inf}$	8.020±0.042	8.063±0.040	0.96	0.87-1.06
LNC_{max}	6.386±0.049	6.419±0.049	0.97	0.86-1.09

Test Product: N = 27 for AUC_{0-t}, $LNAUC_{0-t}$, C_{max}, LNC_{max}, and T_{max}

N = 26 for AUC_{0-inf}, $LNAUC_{0-inf}$, Rate Constant, and Half-life

Reference Product: N = 27 for all parameters

Table 3

Test/Reference Ratios for Pharmacokinetic Parameters for Individual Subjects

Subject	Period	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	1	1.142	1.112	1.124
2	2	1.049	1.022	0.928
3	2	0.569	0.600	0.545
4	1	1.618	1.604	0.811
5	1	0.621	0.679	0.581
6	2	0.836	-	1.311
7	2	0.717	0.661	0.716
8	1	0.869	0.814	0.870
10	1	1.829	1.554	1.821
11	2	1.585	1.188	1.762
12	1	0.616	0.651	0.706
13	1	1.018	1.025	1.157
16	2	0.799	0.813	0.769
17	2	0.953	1.007	0.866
18	1	1.103	1.103	1.324
19	2	1.098	1.071	0.977
20	1	0.922	0.920	0.754
21	2	0.475	0.744	0.699
22	1	1.486	1.533	1.629
23	2	1.252	1.254	1.594
24	1	0.939	0.943	0.834
25	1	1.606	1.530	1.390
26	2	0.577	0.602	0.620
27	2	0.845	0.968	1.038
28	1	0.824	0.812	0.741
29	2	1.206	1.164	1.469
30	1	0.764	0.765	0.738
Mean		1.012	1.005	1.029
Std Deviation		0.361	0.302	0.379
CV		35.63	30.09	36.84

Table 4

AUC_{o-t}/AUC_{0-inf} Ratio for Individual Subjects

Subject	AUC_{o-t}/AUC_{o-inf} Ratio	
	Test	Reference
1	0.93	0.91
2	0.94	0.92
3	0.89	0.94
4	0.80	0.80
5	0.79	0.87
6	-	0.86
7	0.82	0.76
8	0.90	0.84
10	0.91	0.77
11	0.87	0.66
12	0.88	0.93
13	0.92	0.92
16	0.92	0.93
17	0.86	0.91
18	0.89	0.89
19	0.91	0.89
20	0.92	0.92
21	0.55	0.86
22	0.85	0.87
23	0.84	0.85
24	0.92	0.92
25	0.94	0.90
26	0.85	0.89
27	0.82	0.93
28	0.94	0.92
29	0.94	0.91
30	0.91	0.92

Table 5

Formulation of Acyclovir Capsules, 200 mg

Ingredient	Amount mg/cap	Amount w/w %
Acyclovir USP	200.0	48.8
Lactose Monohydrate NF	(b)4 - Confidential Business	
(b)4 -		
Purified Water USP		
Starch NF (b)4 -		
Sodium Lauryl Sulfate NF		
Lactose Monohydrate NF		
(b)4 -		
Magnesium Stearate NF		
Total		
Avg Capsule Fill Wt.	410.0	100.0

#1 White opaque cap/white opaque body hard gelatin capsule with an average weight of 77 mg and composed of: Gelatin NF, Silicon Dioxide NF, Sodium Lauryl Sulfate NF, and Titanium Dioxide

* used during manufacturing process but does not appear in final product

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Capsules
Dose Strength: 200 mg
ANDA No.: 74-674
Firm: Zenith Laboratories Inc.
Submission Date: May 22, 1995
File Name: 74674SD.595

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications: NLT (b)4 (Q) in 60 minutes*
Reference Drug: Zovirax Capsules (Burroughs Wellcome)
Assay Methodology (b)4

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # ND-244 Strength(mg) 200			Reference Product Lot # 4N2584 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	47.5	(b)4 - Confidential Business	25.5	44.2	(b)4 - Confidential Business	29.3
20	85.7		9.0	100.6		2.7
30	92.8		6.1	102.4		2.0
45	98.3		3.9	102.1		1.8
60	101.2		1.2	102.2		2.0

* Agency's specifications: NLT (b)4 (Q) in 30 minutes
Dissolution results of Zenith's individual capsules at 30 minutes: 94.0, 90.6, 99.4, 92.0, 83.6, 93.3, 100.3, 95.9, 92.7, 96.5, 93.9, and 81.3.

Figure 1: Mean Acyclovir Plasma Levels

n = 27

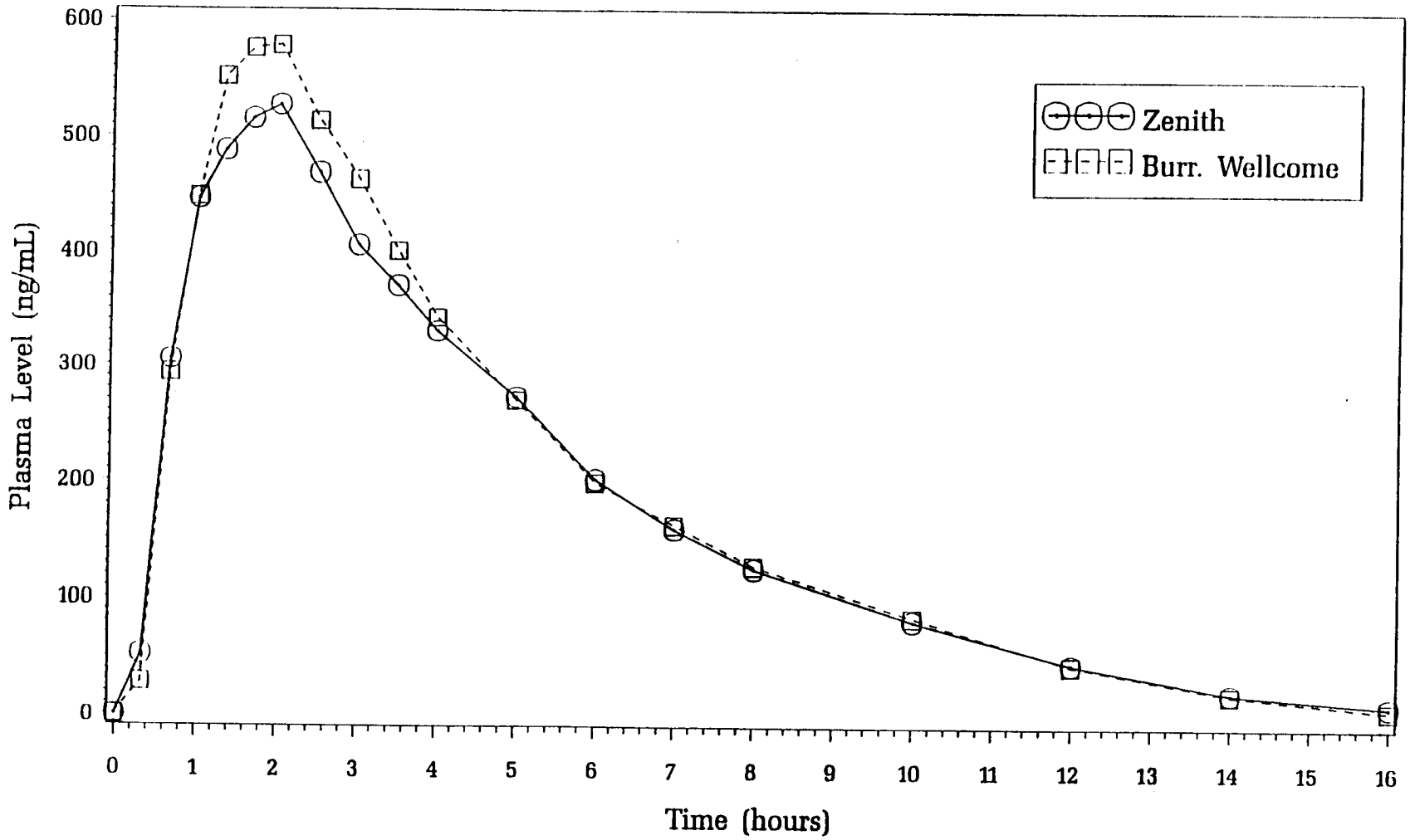


figure 1